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L3 2 DUP REMOVE L2 (0 DUPLICATES REMOVED)

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L3 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2001 BIOSIS
2001:339372 Document No.: PREV200100339372. Nucleic acid molecules encoding glycoprotein VI and recombinant uses thereof. Busfield, Samantha J.; Villeval, Jean-Luc (1). (1) Needham, MA USA. ASSIGNEE: Millennium Pharmaceuticals, Inc.. Patent Info.: US 6245527 June 12, 2001. Official Gazette of the United States Patent and Trademark Office Patents, (June 12, 2001) Vol. 1247, No. 2, pp. No Pagination. e-file. ISSN: 0098-1133. Language: English.

AB The invention provides isolated **TANGO 268** nucleic acid molecules and polypeptide molecules. **TANGO 268** encodes a polypeptide that represents glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The invention also provides antisense nucleic acid molecules, expression vectors containing the nucleic acid molecules of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid molecule of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and **antibodies**. Diagnostic, screening and therapeutic methods utilizing compositions of the invention are also provided.

L3 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
2001:12605 Document No. 134:81775 Glycoprotein VI cDNA and protein from human and murine blood platelets and their diagnostic and therapeutic

applications. Busfield, Samantha J.; Villelal, Jean-luc; Jandrot-Perrus, Martine; Vaincher[redacted]er, William; Gill, Davinder Sin[redacted] Qian, Ming Diana; Kingsbury, Gillian (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2001000810 A1 20010104, 227 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2.
APPLICATION: WO 2000-US18152 20000630. PRIORITY: US 1999-345468 19990630;
US 1999-454824 19991206; US 2000-503387 20000214.

AB The invention provides isolated cDNA mols. and polypeptide mols. that encode human and murine glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The protein initially designated **TANGO 268** represents the platelet-expressed collagen receptor glycoprotein VI (GPVI) based on the following evidence: (1) the glycosylated mol. wts. of **TANGO 268** and GPVI are identical or similar; (2) both are recognized by anti-GPVI **antibodies** and bind to convulxin; (3) both are preferentially expressed in megakaryocytic cells; (4) both ar predicted to have a single N-glycosylation site; (5) the mol. mass of GPVI upon N- and O-linked glycosylation is .apprx.62 kDa, that of GPVI; (6) two Ig-like domains in **TANGO 268** indicates interaction with FcR.gamma.; (7) the absence of a large intracytoplasmic tail suggests that this membrane-bound glycoprotein has no signaling role but assocs. with another member of the Ig family; and (8) **TANGO 268** has a charged arginine residue in the transmembrane domain which is also predicted to be present in GPVI. The human gene for GPVI was mapped on radiation hybrid panels to the long arm of chromosome 19, in the region 19q13, syntenic to mouse chromosome 7. The invention also provides antisense nucleic acid mols., expression vectors contg. the nucleic acid mols. of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid mol. of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and **antibodies**. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

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one before and one after the expression you are setting
off or masking.

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L5 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2001 ACS
2001:12605 Document [redacted] 134:81775 Glycoprotein VI cD[redacted] and protein from human and murine blood platelets and their diagnostic and therapeutic applications. Busfield, Samantha J.; Villelal, Jean-luc; Jandrot-Perrus, Martine; Vainchencker, William; Gill, Davinder Singh; Qian, Ming Diana; Kingsbury, Gillian (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2001000810 A1 20010104, 227 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US18152 20000630. PRIORITY: US 1999-345468 19990630;
US 1999-454824 19991206; US 2000-503387 20000214.

AB The invention provides isolated cDNA mols. and polypeptide mols. that encode human and murine glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The protein initially designated TANGO 268 represents the platelet-expressed collagen receptor glycoprotein VI (GPVI) based on the following evidence: (1) the glycosylated mol. wts. of TANGO 268 and GPVI are identical or similar; (2) both are recognized by **anti-GPVI antibodies** and bind to convulxin; (3) both are preferentially expressed in megakaryocytic cells; (4) both ar predicted to have a single N-glycosylation site; (5) the mol. mass of GPVI upon N- and O-linked glycosylation is .apprx.62 kDa, that of GPVI; (6) two Ig-like domains in TANGO 268 indicates interaction with FcR.gamma.; (7) the absence of a large intracytoplasmic tail suggests that this membrane-bound glycoprotein has no signaling role but assocs. with another member of the Ig family; and (8) TANGO 268 has a charged arginine residue in the transmembrane domain which is also predicted to be present in GPVI. The human gene for GPVI was mapped on radiation hybrid panels to the long arm of chromosome 19, in the region 19q13, syntenic to mouse chromosome 7. The invention also provides antisense nucleic acid mols., expression vectors contg. the nucleic acid mols. of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid mol. of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and **antibodies**. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

L5 ANSWER 2 OF 10 MEDLINE DUPLICATE 1
2001436540 Document Number: 21359356. PubMed ID: 11344165. A novel viper venom metalloproteinase, alborhagin, is an agonist at the platelet collagen receptor GPVI. Andrews R K; Gardiner E E; Asazuma N; Berlanga O; Tulasne D; Nieswandt B; Smith A I; Berndt M C; Watson S P. (Hazel and Pip Appel Vascular Biology Laboratory and the Peptide Biology Laboratory, Baker Medical Research Institute, Melbourne 8008, Australia.. rkandrews@hotmail.com) . JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jul 27) 276 (30) 28092-7. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The interaction of platelet membrane glycoprotein VI (GPVI) with collagen can initiate (patho)physiological thrombus formation. The viper venom C-type lectin family proteins convulxin and alboaggregin-A activate platelets by interacting with GPVI. In this study, we isolated from white-lipped tree viper (Trimeresurus albolabris) venom, alborhagin, which is functionally related to convulxin because it activates platelets but is

structurally different and related to venom metalloproteinases. Alborhagin-induced platelet aggregation (EC50, <7.[redacted]microg/ml) was inhibitable by an anti-alphaIIbbeta3 **antibody**, CRC64, and the Src family kinase inhibitor PP1, suggesting that alborhagin activates platelets, leading to alphaIIbbeta3-dependent aggregation. Additional evidence suggested that, like convulxin, alborhagin activated platelets by a mechanism involving GPVI. First, alborhagin- and convulxin-treated platelets showed a similar tyrosine phosphorylation pattern, including a similar level of phospholipase Cgamma2 phosphorylation. Second, alborhagin induced GPVI-dependent responses in GPVI-transfected K562 and Jurkat cells. Third, alborhagin-dependent aggregation of mouse platelets was inhibited by the **anti-GPVI** monoclonal **antibody** JAQ1. Alborhagin had minimal effect on convulxin binding to GPVI-expressing cells, indicating that these venom proteins may recognize distinct binding sites. Characterization of alborhagin as a GPVI agonist that is structurally distinct from convulxin demonstrates the versatility of snake venom toxins and provides a novel probe for GPVI-dependent platelet activation.

L5 ANSWER 3 OF 10 MEDLINE DUPLICATE 2
2001370835 Document Number: 21226781. PubMed ID: 11278467. Expression and function of the collagen receptor GPVI during megakaryocyte maturation.
Lagrue-Lak-Hal A H; Debili N; Kingbury G; Lecut C; Le Couedic J P; Villeval J L; Jandrot-Perrus M; Vainchenker W. (INSERM E9907, Faculte Xavier Bichat, 75870 Paris Cedex 18, Paris, France.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 May 4) 276 (18) 15316-25. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB In this report, the expression and function of the platelet collagen receptor glycoprotein VI (GPVI) were studied in human megakaryocytes during differentiation and maturation of mobilized blood and cord blood derived CD34(+) cells. By flow cytometry, using an **anti-GPVI** monoclonal **antibody** or convulxin, a GPVI-specific ligand, GPVI was detected only on CD41(+) cells including some CD41(+)/CD34(+) cells, suggesting expression at a stage of differentiation similar to CD41. These results were confirmed at the mRNA level using reverse transcription-polymerase chain reaction. GPVI expression was low during megakaryocytic differentiation but increased in the more mature megakaryocytes (CD41(high)). As in platelets, megakaryocyte GPVI associates with the Fc receptor gamma chain (FcRgamma). The FcR gamma chain was detected at the RNA and protein level at all stages of megakaryocyte maturation preceding the expression of GPVI. The other collagen receptor, alpha(2)beta(1) integrin (CD49b/CD29), had a pattern of expression similar to GPVI. Megakaryocytic GPVI was recognized as a 55-kDa protein by immunoblotting and ligand blotting, and thus it presented a slightly lower apparent molecular mass than platelet GPVI (58 kDa). Megakaryocytes began to adhere to immobilized convulxin via GPVI after only 8-10 days of culture, at a time when megakaryocytes were maturing. At this stage of maturation, they also adhered to immobilized collagen by alpha(2)beta(1) integrin-dependent and -independent mechanisms. Convulxin induced a very similar pattern of protein tyrosine phosphorylation in megakaryocytes and platelets including Syk, FcRgamma, and PLC(gamma)2. Our results showed that GPVI is expressed early during megakaryocytic differentiation but functionally allows megakaryocyte adherence to collagen only at late stages of differentiation when its expression increases.

L5 ANSWER 4 OF 10 MEDLINE DUPLICATE 3
2001446261 Document Number: 21384761. PubMed ID: 11493449. Platelet glycoprotein V binds to collagen and participates in platelet adhesion and aggregation. Moog S; Mangin P; Lenain N; Strassel C; Ravanat C; Schuhler S; Freund M; Santer M; Kahn M; Nieswandt B; Gachet C; Cazenave J P; Lanza F. (INSERM U.311, Etablissement Francais du Sang-Alsace, Strasbourg, France.) BLOOD, (2001 Aug 15) 98 (4) 1038-46. Journal code: A8G; 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.
AB Glycoprotein V (GPV) is a subunit of the platelet GPIb-V-IX receptor for von Willebrand factor and thrombin. GPV is cleaved from the platelet surface during activation by thrombin, but its role in hemostasis is still unknown. It is reported that GPV knockout mice had a decreased tendency to form arterial occluding thrombi in an intravital thrombosis model and abnormal platelet interaction with the subendothelium. In vitro, GPV-deficient platelets exhibited defective adhesion to a collagen type I-coated surface under flow or static conditions. Aggregation studies demonstrated a decreased response of the GPV-deficient platelets to collagen, reflected by an increased lag phase and reduced amplitude of aggregation. Responses to adenosine diphosphate, arachidonic acid, and the thromboxane analog U46619 were normal but were enhanced to low thrombin concentrations. The defect of GPV null platelets made them more sensitive to inhibition by the **anti-GPVI** monoclonal **antibody** (mAb) JAQ1, and this was also the case in aspirin- or apyrase-treated platelets. Moreover, an mAb (V.3) against the extracellular domain of human GPV selectively inhibited collagen-induced aggregation in human or rat platelets. V.3 injected in rats as a bolus decreased the ex vivo collagen aggregation response without affecting the platelet count. Finally, surface plasmon resonance studies demonstrated binding of recombinant soluble GPV on a collagen-coupled matrix. In conclusion, GPV binds to collagen and appears to be required for normal platelet responses to this agonist. (Blood. 2001;98:1038-1046)

L5 ANSWER 5 OF 10 MEDLINE DUPLICATE 4
2001388659 Document Number: 21335840. PubMed ID: 11443641. **Antibody** against platelet membrane glycoprotein VI in a patient with systemic lupus erythematosus. Takahashi H; Moroi M. (Department of Internal Medicine, Niigata Prefectural Kamo Hospital, Kamo, Niigata, Japan.) AMERICAN JOURNAL OF HEMATOLOGY, (2001 Aug) 67 (4) 262-7. Journal code: 3H4; 7610369. ISSN: 0361-8609. Pub. country: United States. Language: English.
AB Platelet-collagen interaction is important in primary hemostasis and collagen receptors on the platelet surface include membrane glycoprotein (GP) Ia/IIa and VI. Platelets from a 47-year-old woman with systemic lupus erythematosus (SLE) and a mild bleeding symptom showed a defective collagen-induced aggregation and an impaired adhesion to collagen surface. The patient's platelets had a markedly decreased content of GPVI. The patient had an **antibody** against GPVI in serum and the patient's plasma induced aggregation and release reaction of normal platelets. These findings indicate that GPVI is an important receptor for collagen on the platelet surface, and that **anti-GPVI antibody** activates the platelets, resulting in aggregation. This is the first documented case of SLE who acquired a platelet-aggregating **anti-GPVI antibody**.

L5 ANSWER 6 OF 10 BIOSIS COPYRIGHT 2001 BIOSIS

2001:311599 Document No.: PREV200100311599. Long-term antithrombotic protection by irreversible inactivation of platelet glycoprotein VI in mice. Nieswandt, Bernhard (1); Schulte, Valerie (1); Bergmeier, Wolfgang (1); Mokhtari-Nejad, Rabee (1); Cazenave, Jean P.; Gachet, Christian; Zirngibl, Hubert (1). (1) Molecular Oncology, Witten/Herdecke University, Wuppertal Germany. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 269a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology. ISSN: 0006-4971. Language: English. Summary Language: English.

AB Coronary artery thrombosis is often initiated by abrupt disruption of the atherosclerotic plaque followed by deposition and activation of platelets on the subendothelial layers in the disrupted plaque. Because the extracellular matrix protein collagen is the most thrombogenic constituent of the subendothelial layer, a selective inhibition of the collagen activation pathway in platelets may provide strong antithrombotic protection while preserving other platelet functions. Growing evidence suggests that platelet glycoprotein (GP) VI is the major collagen receptor for platelet activation making this receptor a good candidate for such a specific inhibition. In the current study, we have investigated the antithrombotic effects of the first monoclonal **antibody** (mAb) against mouse GPVI (JAQ1, Nieswandt et al; 2000, J Biol Chem, 275(31):23998-24002). Injection of 100 mug JAQ1 only had mild and transient effects on platelet counts with a maximum drop of approximately 34 +- 7.4 % on day 1 and a return to normal after 2-3 days. JAQ1 pretreated mice were completely protected against lethal thromboembolism induced by infusion of a mixture of collagen (0.8 mg/kg) and epinephrine (60 mug/kg) for at least two weeks (100% survivors on days 3, 7, and 14 after mAb injection, n=8 per group, 5% survivors in the control group, n=20). Aggregometric and flow cytometric studies demonstrated that platelets from JAQ1 treated mice were completely resistant against activation with high concentrations of collagen (up to 50 mug/ml) and collagen related peptides (up to 100 mug/ml) ex vivo on days 3, 7, and 14. In JAQ1 treated mice, GPVI was not detectable in a Western blot analysis of platelet lysates for minimally two weeks, suggesting irreversible inactivation (or degradation) of the receptor on circulating platelets. In contrast to collagen, other agonists, such as ADP or platelet aggregating agents, such as PMA induced normal activation and aggregation of these platelets. Consequently, the tail bleeding times were only moderately increased in **anti-GPVI** treated mice compared to control mice on day 3, 7, and 14. These results establish GPVI as an attractive target for long-term antithrombotic therapy.

L5 ANSWER 7 OF 10 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

1999163586 EMBASE Function of glycoprotein VI and integrin .alpha.2.beta.1 in the procoagulant response of single, collagen-adherent platelets. Heemskerk J.W.M.; Siljander P.; Vuist W.M.; Breikers G.; Reutelingsperger C.P.M.; Barnes M.J.; Knight C.G.; Lassila R.; Farndale R.W.. Dr. J.W.M. Heemskerk, Department of Biochemistry, University of Maastricht, PO Box 616, 6200 MD Maastricht, Netherlands. JWM.Heemskerk@Bioch.UniMaas.nl. Thrombosis and Haemostasis 81/5 (782-792) 1999.
Refs: 47.
ISSN: 0340-6245. CODEN: THHADQ. Pub. Country: Germany. Language: English. Summary Language: English.

AB Various collagen-based materials were used to assess the structural requirements of collagen for inducing the procoagulant response of adhering platelets, as well as the collagen receptors involved. Crosslinked or monomeric collagen-related peptide (CRP),

Gly-Cys-Hyp-(Gly-Pro-Hyp)10-Gly-Cys-Hyp-Gly was highly adhesive for platelets in a glycoprotein VI- (GpVI-)dependent manner. Adhesion was followed by a prolonged increase in cytosolic [Ca2+](i), formation of membrane blebs, exposure of phosphatidylserine (PS and generation of prothrombinase-stimulating activity. Fibrils of type-I collagen were less adhesive but, once adhered, many of the platelets presented a full procoagulant response. Monomeric type-I collagen was unable to support adhesion, unless Mg2+-dependent integrin .alpha.2.beta.1 interactions were facilitated by omission of Ca2+ ions. With all surfaces, however, post-addition of CaCl2 to adhering platelets resulted in a potent Ca2+-influx signal, followed by PS exposure and bleb formation. The procoagulant response elicited by binding to CRP was inhibited by **anti-GpVI** Fab fragments, but not by impeding integrin .alpha.2.beta.1-mediated events. With fibrillar collagen, it was inhibited by blocking either the GpVI- or integrin .alpha.2.beta.1 mediated interactions. This suggests that the triple-helical Gly-Pro-Hyp repeat in CRP and analogous sequences in fibrillar collagen stimulate the procoagulant response of adherent platelets by acting as ligands for GpVI. Influx of Ca2+ is required for this response, and adhesion via integrin .alpha.2.beta.1 serves to potentiate the signaling effects of GpVI.

L5 ANSWER 8 OF 10 MEDLINE DUPLICATE 5

1998136126 Document Number: 98136126. PubMed ID: 9468482. Platelet adhesion to native type I collagen fibrils. Role of GPVI in divalent cation-dependent and -independent adhesion and thromboxane A2 generation. Nakamura T; Jamieson G A; Okuma M; Kambayashi J; Tandon N N. (Otsuka America Pharmaceutical Inc., Rockville, Maryland 20850, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Feb 20) 273 (8) 4338-44. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Three glycoproteins (GPs), namely GPIa-IIa, GPVI, and GPIV, have been recently implicated in platelet-collagen adhesive interactions. We have employed **antibodies** to these GPs to investigate further their role in platelet adhesion to immobilized monomeric and polymeric fibrillar collagen under static conditions in the presence and the absence of Mg2+. In the presence of Mg2+, each **antibody** inhibited platelet adhesion to fibrillar collagen from 70 to 85%, especially during the early phase (<15 min), but the inhibitory effects diminished dramatically to 25% or less by 60 min. Combination of **anti-GPVI** with anti-GPIa-IIa **antibodies** completely inhibited platelet adhesion at 60 min. Anti-GPIV and anti-GPIa-IIa or **anti-GPVI** **antibodies** in combinations were more effective in inhibiting adhesion than was anti-GPIa-IIa or **anti-GPVI** alone. In the absence of Mg2+, **anti-GPVI** completely inhibited adhesion at 60 min, while anti-GPIV **antibody** inhibited adhesion by about 50% and minimal effects were seen with anti-GPIa-IIa, suggesting that GPIa-IIa does not play a significant role in the divalent cation-independent platelet adhesion to immobilized fibrillar collagen. Under either divalent cation-dependent or -independent conditions, platelets adhered to fibrillar collagen were able to secrete contents of both alpha-granules and dense granules and generate thromboxane A2 (TXA2), but platelets adhering to acid soluble monomeric collagen neither secreted their granular contents nor generated TXA2. Although **anti-GPVI antibodies** were not able to inhibit Mg2+-dependent adhesion, they completely inhibited TXA2 generation under both divalent cation-dependent and -independent conditions. With the other

antibodies, TXA2 generation corresponded with the amount of adhesion observed. These results suggest that GPVI is directly associated with the TXA2 generating system during platelet-collagen interaction.

L5 ANSWER 9 OF 10 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6
1998228355 EMBASE Convulxin-induced platelet adhesion and aggregation: Involvement of glycoproteins VI and IaIIa. Jandrot-Perrus M.; Lagrue A.H.;
Leduc M.; Okuma M.; Bon C.. Dr. M. Jandrot-Perrus, Lab. Recherche Hemostase Thrombose, Faculte de Medecine Xavier Bichat, 75870 Paris Cedex 18, France. Platelets 9/3-4 (207-211) 1998.
Refs: 22.
ISSN: 0953-7104. CODEN: PLTEEF. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB The interaction of convulxin (Cvx), a 72-kDa glycoprotein isolated from the venom of Crotalus durissus terrificus with human platelets has been studied. Cvx at low concentrations (below 100 pM) induced platelet aggregation, dense body secretion and intracellular calcium mobilization which indicates that Cvx is a potent activator of human platelets. Cvx-induced platelet aggregation and secretion was inhibited by 6F1 an anti-integrin .alpha.2.beta.1 monoclonal **antibody** that was without effect on calcium mobilization. **Anti-GPVI** Fab fragments inhibited aggregation, secretion and calcium mobilization triggered by Cvx. In addition, immobilized Cvx was found to induce divalent cation-independent platelet adhesion in a static system. Platelet adhesion to Cvx was inhibited by **anti-GPVI** Fab fragments but not by anti-integrin .alpha.2.beta.1. Cvx was shown to bind to a 57,000 Dalton protein that was identified as GPVI. Altogether, these results indicate that GPVI behaves as a receptor for Cvx, while integrin .alpha.2.beta.1 could play a regulatory role in Cvx-induced platelet aggregation. Cvx and collagen interaction with platelets, thus appears to share some characteristics but to also have specific properties.

L5 ANSWER 10 OF 10 MEDLINE DUPLICATE 7
1998001677 Document Number: 98001677. PubMed ID: 9341142. Adhesion and activation of human platelets induced by convulxin involve glycoprotein VI and integrin alpha2beta1. Jandrot-Perrus M; Lagrue A H; Okuma M; Bon C. (Laboratoire de Recherche sur l'Hemostase et la Thrombose, Faculte de Medecine Xavier Bichat, BP 416, 75870 Paris Cedex 18, France.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Oct 24) 272 (43) 27035-41. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB We analyzed the interaction of convulxin (Cvx), a 72-kDa protein isolated from the venom of Crotalus durissus terrificus, with human platelets. Cvx is a potent platelet agonist that induces an increase in the intracellular Ca2+ concentration ([Ca2+]i), granule exocytosis and aggregation. 125I-Labeled Cvx binds specifically and rapidly to platelets at binding sites of high and moderate affinity. Platelets adhere to immobilized Cvx in a time-dependent but cation-independent manner. Platelet exocytosis and aggregation induced by Cvx were inhibited by an anti-integrin alpha2beta1 monoclonal **antibody** (6F1) and by the Fab fragments of a polyclonal anti-glycoprotein VI (GPVI) **antibody**. Both the adhesion of platelets to Cvx and the Cvx-induced increase in [Ca2+]i were inhibited by **anti-GPVI** Fab fragments but not by 6F1. Ligand blotting assay showed that 125I-Cvx binds to a 57-kDa platelet protein with an electrophoretic mobility identical to that of GPVI. In addition, we observed the following: (i) 125I-Cvx binds to GPVI immunoprecipitated by the **anti-GPVI antibody**

from a platelet lysate, and (ii) Cvx inhibits the binding of **anti -GPVI** IgG to GPVI. Taken together, these results demonstrate that GPVI behaves as a Cvx receptor and that the alpha2beta1 integrin appears to be involved in the later stages of Cvx-induced platelet activation, i.e. exocytosis and aggregation.

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(FILE 'HOME' ENTERED AT 08:13:17 ON 19 NOV 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 08:13:41 ON 19 NOV 2001

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L1      2241411 S ANTIBODY
L2            2 S L1 AND "TANGO 268"
L3            2 DUP REMOVE L2 (0 DUPLICATES REMOVED)
L4           33 S L1 AND "ANTI-GPVI"
L5           10 DUP REMOVE L4 (23 DUPLICATES REMOVED)
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L2   ANSWER 1 OF 2  BIOSIS  COPYRIGHT 2001 BIOSIS
AN   2001:339372  BIOSIS
DN   PREV200100339372
TI   Nucleic acid molecules encoding glycoprotein VI and recombinant uses
     thereof.
AU   Busfield, Samantha J.; Villeval, Jean-Luc (1)
CS   (1) Needham, MA USA
     ASSIGNEE: Millennium Pharmaceuticals, Inc.
PI   US 6245527 June 12, 2001
SO   Official Gazette of the United States Patent and Trademark Office
Patents,
     (June 12, 2001) Vol. 1247, No. 2, pp. No Pagination. e-file.
     ISSN: 0098-1133.
DT   Patent
LA   English
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=> d l2 1-2 cbib abs

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L2   ANSWER 1 OF 2  BIOSIS  COPYRIGHT 2001 BIOSIS
2001:339372  Document No.: PREV200100339372. Nucleic acid molecules encoding
     glycoprotein VI and recombinant uses thereof. Busfield, Samantha J.;
     Villeval, Jean-Luc (1). (1) Needham, MA USA. ASSIGNEE: Millennium
     Pharmaceuticals, Inc.. Patent Info.: US 6245527 June 12, 2001. Official
     Gazette of the United States Patent and Trademark Office Patents, (June
     12, 2001) Vol. 1247, No. 2, pp. No Pagination. e-file. ISSN: 0098-1133.
     Language: English.
AB   The invention provides isolated TANGO 268 nucleic acid
     molecules and polypeptide molecules. TANGO 268 encodes
     a polypeptide that represents glycoprotein VI, a platelet membrane
     glycoprotein that is involved platelet-collagen interactions. The
     invention also provides antisense nucleic acid molecules, expression
     vectors containing the nucleic acid molecules of the invention, host
cells
     into which the expression vectors have been introduced, and non-human
     transgenic animals in which a nucleic acid molecule of the invention has
     been introduced or disrupted. The invention still further provides
     isolated polypeptides, fusion polypeptides, antigenic peptides and
     antibodies. Diagnostic, screening and therapeutic methods
     utilizing compositions of the invention are also provided.
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L2 ANSWER 2 OF 2 CA[redacted]S COPYRIGHT 2001 ACS
2001:12605 Document [redacted]: 134:81775 Glycoprotein VI cDNA and protein from human and murine blood platelets and their diagnostic and therapeutic applications. Busfield, Samantha J.; Villelal, Jean-luc; Jandrot-Perrus, Martine; Vainchencker, William; Gill, Davinder Singh; Qian, Ming Diana; Kingsbury, Gillian (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2001000810 A1 20010104, 227 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US18152 20000630. PRIORITY: US 1999-345468 19990630;
US 1999-454824 19991206; US 2000-503387 20000214.

AB The invention provides isolated cDNA mols. and polypeptide mols. that encode human and murine glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The protein initially designated **TANGO 268** represents the platelet-expressed collagen receptor glycoprotein VI (GPVI) based on the following evidence: (1) the glycosylated mol. wts. of **TANGO 268** and GPVI are identical or similar; (2) both are recognized by anti-GPVI **antibodies** and bind to convulxin; (3) both are preferentially expressed in megakaryocytic cells; (4) both ar predicted to have a single N-glycosylation site; (5) the mol. mass of GPVI upon N- and O-linked glycosylation is .apprx.62 kDa, that of GPVI; (6) two Ig-like domains in **TANGO 268** indicates interaction with FcR.gamma.; (7) the absence of a large intracytoplasmic tail suggests that this membrane-bound glycoprotein has no signaling role but assocs. with another member of the Ig family; and (8) **TANGO 268** has a charged arginine residue in the transmembrane domain which is also predicted to be present in GPVI. The human gene for GPVI was mapped on radiation hybrid panels to the long arm of chromosome 19, in the region 19q13, syntenic to mouse chromosome 7. The invention also provides antisense nucleic acid mols., expression vectors contg. the nucleic acid mols. of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid mol. of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and **antibodies**. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

=> s l1 and convluxin

L6 0 L1 AND CONVLUXIN

=> s l1 and convulxin

L7 60 L1 AND CONVULXIN

=> dup remove l7

PROCESSING COMPLETED FOR L7
L8 18 DUP REMOVE L7 (42 DUPLICATES REMOVED)

=> d l8 1-18 cbib abs

L8 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2001 ACS

2001:12605 Document No. 134:81775 Glycoprotein VI cDNA and protein from human and murine blood platelets and their diagnostic and therapeutic applications. Busfield, Samantha J.; Villelal, Jean-luc; Jandrot-Perrus, Martine; Vainchencker, William; Gill, Davinder Singh; Qian, Ming Diana; Kingsbury, Gillian (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2001000810 A1 20010104, 227 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US18152 20000630. PRIORITY: US 1999-345468 19990630;
US 1999-454824 19991206; US 2000-503387 20000214.

AB The invention provides isolated cDNA mols. and polypeptide mols. that encode human and murine glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The protein initially designated TANGO 268 represents the platelet-expressed collagen receptor glycoprotein VI (GPVI) based on the following evidence: (1) the glycosylated mol. wts. of TANGO 268 and GPVI are identical or similar; (2) both are recognized by anti-GPVI **antibodies** and bind to **convulxin**; (3) both are preferentially expressed in megakaryocytic cells; (4) both ar predicted to have a single N-glycosylation site; (5) the mol. mass of GPVI upon N- and O-linked glycosylation is .apprx.62 kDa, that of GPVI; (6) two Ig-like domains in TANGO 268 indicates interaction with FcR.gamma.; (7) the absence of a large intracytoplasmic tail suggests that this membrane-bound glycoprotein has no signaling role but assocs. with another member of the Ig family; and (8) TANGO 268 has a charged arginine residue in the transmembrane domain which is also predicted to be present in GPVI. The human gene for GPVI was mapped on radiation hybrid panels to the long arm of chromosome 19, in the region 19q13, syntenic to mouse chromosome 7. The invention also provides antisense nucleic acid mols., expression vectors contg. the nucleic acid mols. of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid mol. of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and **antibodies**. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

L8 ANSWER 2 OF 18 MEDLINE DUPLICATE 1

2001436540 Document Number: 21359356. PubMed ID: 11344165. A novel viper venom metalloproteinase, alborhagin, is an agonist at the platelet collagen receptor GPVI. Andrews R K; Gardiner E E; Asazuma N; Berlanga O; Tulasne D; Nieswandt B; Smith A I; Berndt M C; Watson S P. (Hazel and Pip Appel Vascular Biology Laboratory and the Peptide Biology Laboratory, Baker Medical Research Institute, Melbourne 8008, Australia.. rkandrews@hotmail.com) . JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jul 27) 276 (30) 28092-7. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The interaction of platelet membrane glycoprotein VI (GPVI) with collagen can initiate (patho)physiological thrombus formation. The viper venom C-type lectin family proteins **convulxin** and alboaggregin-A activate platelets by interacting with GPVI. In this study, we isolated from white-lipped tree viper (Trimeresurus albolabris) venom, alborhagin,

which is functionally related to **convulxin** because it activates platelets but is [redacted]ucturally different and relate[redacted]o venom metalloproteinases. Alborhagin-induced platelet agg[redacted]gation (EC50, <7.5 microg/ml) was inhibitable by an anti-alphaIIbbeta3 **antibody**, CRC64, and the Src family kinase inhibitor PP1, suggesting that alborhagin activates platelets, leading to alphaIIbbeta3-dependent aggregation. Additional evidence suggested that, like **convulxin**, alborhagin activated platelets by a mechanism involving GPVI. First, alborhagin- and **convulxin**-treated platelets showed a similar tyrosine phosphorylation pattern, including a similar level of phospholipase Cgamma2 phosphorylation. Second, alborhagin induced GPVI-dependent responses in GPVI-transfected K562 and Jurkat cells. Third, alborhagin-dependent aggregation of mouse platelets was inhibited by the anti-GPVI monoclonal **antibody** JAQ1. Alborhagin had minimal effect on **convulxin** binding to GPVI-expressing cells, indicating that these venom proteins may recognize distinct binding sites. Characterization of alborhagin as a GPVI agonist that is structurally distinct from **convulxin** demonstrates the versatility of snake venom toxins and provides a novel probe for GPVI-dependent platelet activation.

L8 ANSWER 3 OF 18 MEDLINE DUPLICATE 2
2001350473 Document Number: 21293088. PubMed ID: 11287424. Aggretin, a heterodimeric C-type lectin from Calloselasma rhodostoma (malayan pit viper), stimulates platelets by binding to alpha 2beta 1 integrin and glycoprotein Ib, activating Syk and phospholipase Cgamma 2, but does not involve the glycoprotein VI/Fc receptor gamma chain collagen receptor. Navdaev A; Clemetson J M; Polgar J; Kehrel B E; Glauner M; Magnenat E; Wells T N; Clemetson K J. (Theodor Kocher Institute, University of Berne, Freiestrasse 1, CH-3012 Berne, Switzerland.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jun 15) 276 (24) 20882-9. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Aggretin, a potent platelet activator, was isolated from Calloselasma rhodostoma venom, and 30-amino acid N-terminal sequences of both subunits were determined. Aggretin belongs to the heterodimeric snake C-type lectin family and is thought to activate platelets by binding to platelet glycoprotein alpha(2)beta(1). We now show that binding to glycoprotein (GP) Ib is also required. Aggretin-induced platelet activation was inhibited by a monoclonal **antibody** to GPIb as well as by **antibodies** to alpha(2)beta(1). Binding of both of these platelet receptors to aggretin was confirmed by affinity chromatography. No binding of other major platelet membrane glycoproteins, in particular GPVI, to aggretin was detected. Aggretin also activates platelets from Fc receptor gamma chain (Fcgamma)-deficient mice to a greater extent than those from normal control mice, showing that it does not use the GPVI/Fcgamma pathway. Platelets from Fcgamma-deficient mice expressed fibrinogen receptors normally in response to collagen, although they did not aggregate, indicating that these platelets may partly compensate via other receptors including alpha(2)beta(1) or GPIb for the lack of the Fcgamma pathway. Signaling by aggretin involves a dose-dependent lag phase followed by rapid tyrosine phosphorylation of a number of proteins. Among these are p72(SYK), p125(FAK), and PLCgamma2, whereas, in comparison with collagen and **convulxin**, the Fcgamma subunit neither is phosphorylated nor coprecipitates with p72(SYK). This supports an independent, GPIb- and integrin-based pathway for activation of p72(SYK) not involving the Fcgamma receptor.

L8 ANSWER 4 OF 18 MEDLINE DUPLICATE 3
2001370835 Document Number: 21226781. PubMed ID: 11278467. Expression and

function of the collagen receptor GPVI during megakaryocyte maturation. Lagrue-Lak-Hal A [redacted] Debili N; Kingbury G; Lecut C; [redacted] Couedic J P; Villeval J L; Jandrot-Perrus M; Vainchenker W. (INSERM E9907, Faculte Xavier Bichat, 75870 Paris Cedex 18, Paris, France.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 May 4) 276 (18) 15316-25. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB In this report, the expression and function of the platelet collagen receptor glycoprotein VI (GPVI) were studied in human megakaryocytes during differentiation and maturation of mobilized blood and cord blood derived CD34(+) cells. By flow cytometry, using an anti-GPVI monoclonal **antibody** or **convulxin**, a GPVI-specific ligand, GPVI was detected only on CD41(+) cells including some CD41(+)/CD34(+) cells, suggesting expression at a stage of differentiation similar to CD41. These results were confirmed at the mRNA level using reverse transcription-polymerase chain reaction. GPVI expression was low during megakaryocytic differentiation but increased in the more mature megakaryocytes (CD41(high)). As in platelets, megakaryocyte GPVI associates with the Fc receptor gamma chain (FcRgamma). The FcR gamma chain was detected at the RNA and protein level at all stages of megakaryocyte maturation preceding the expression of GPVI. The other collagen receptor, alpha(2)beta(1) integrin (CD49b/CD29), had a pattern of expression similar to GPVI. Megakaryocytic GPVI was recognized as a 55-kDa protein by immunoblotting and ligand blotting, and thus it presented a slightly lower apparent molecular mass than platelet GPVI (58 kDa). Megakaryocytes began to adhere to immobilized **convulxin** via GPVI after only 8-10 days of culture, at a time when megakaryocytes were maturing. At this stage of maturation, they also adhered to immobilized collagen by alpha(2)beta(1) integrin-dependent and -independent mechanisms. **Convulxin** induced a very similar pattern of protein tyrosine phosphorylation in megakaryocytes and platelets including Syk, FcRgamma, and PLC(gamma)2. Our results showed that GPVI is expressed early during megakaryocytic differentiation but functionally allows megakaryocyte adherence to collagen only at late stages of differentiation when its expression increases.

L8 ANSWER 5 OF 18 MEDLINE

2001272329 Document Number: 21231159. PubMed ID: 11331578. Glycoprotein VI but not alpha2beta1 integrin is essential for platelet interaction with collagen. Nieswandt B; Brakebusch C; Bergmeier W; Schulte V; Bouvard D; Mokhtari-Nejad R; Lindhout T; Heemskerk J W; Zirngibl H; Fassler R. (Department of Molecular Oncology, General Surgery, Witten/Herdecke University, 42117 Wuppertal, Germany.. nieswand@klinikum-wuppertal.de) . EMBO JOURNAL, (2001 May 1) 20 (9) 2120-30. Journal code: EMB; 8208664. ISSN: 0261-4189. Pub. country: England: United Kingdom. Language: English.

AB Platelet adhesion on and activation by components of the extracellular matrix are crucial to arrest post-traumatic bleeding, but can also harm tissue by occluding diseased vessels. Integrin alpha2beta1 is thought to be essential for platelet adhesion to subendothelial collagens, facilitating subsequent interactions with the activating platelet collagen receptor, glycoprotein VI (GPVI). Here we show that Cre/loxP-mediated loss of beta1 integrin on platelets has no significant effect on the bleeding time in mice. Aggregation of beta1-null platelets to native fibrillar collagen is delayed, but not reduced, whereas aggregation to enzymatically

digested soluble collagen is abolished. Furthermore, beta1-null platelets adhere to fibrillar but not soluble collagen under static as well as low (150 s(-1)) and high (1000 s(-1)) shear flow conditions, probably through binding of alphaIIbbeta3 to von Willebrand factor. On the other hand, we show that platelets lacking GPVI can not activate integrins and consequently fail to adhere to and aggregate on fibrillar as well as soluble collagen. These data show that GPVI plays the central role in platelet-collagen interactions by activating different adhesive receptors, including alpha2beta1 integrin, which strengthens adhesion without being essential.

L8 ANSWER 6 OF 18 MEDLINE DUPLICATE 4

2001112665 Document Number: 20576376. PubMed ID: 11036078. Evidence for two distinct epitopes within collagen for activation of murine platelets. Schulte V; Snell D; Bergmeier W; Zirngibl H; Watson S P; Nieswandt B. (Department of Molecular Oncology, General Surgery, Witten/Herdecke University, 42117 Wuppertal, Germany.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jan 5) 276 (1) 364-8. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB It has recently been shown that the monoclonal **antibody** JAQ1 to murine glycoprotein VI (GPVI) can cause aggregation of mouse platelets upon **antibody** cross-linking and that collagen-induced platelet aggregation can be inhibited by preincubation of platelets with JAQ1 in the absence of cross-linking (Nieswandt, B., Bergmeier, W., Schulte, V., Rackebrandt, K., Gessner, J. E., and Zirngibl, H. (2000) J. Biol. Chem. 275, 23998-24002). In the present study, we have shown that cross-linking of GPVI by JAQ1 results in tyrosine phosphorylation of the same profile of proteins as that induced by collagen, including the Fc receptor (FcR) gamma-chain, Syk, LAT, SLP-76, and phospholipase C gamma 2. In contrast, platelet aggregation and tyrosine phosphorylation of these proteins were inhibited when mouse platelets were preincubated with JAQ1 in the absence of cross-linking and were subsequently stimulated with a collagen-related peptide (CRP) that is specific for GPVI and low concentrations of collagen. However, at higher concentrations of collagen, but not CRP, aggregation of platelets and tyrosine phosphorylation of the above proteins (except for the adapter LAT) is re-established despite the presence of JAQ1. These observations suggest that a second activatory binding site, which is distinct from the CRP binding site on GPVI on mouse platelets, is occupied in the presence of high concentrations of collagen. Although this could be a second site on GPVI that is activated by a novel motif within the collagen molecule, the absence of LAT phosphorylation in response to collagen in the presence of JAQ1 suggests that this is more likely to be caused by activation of a second receptor that is also coupled to the FcR gamma-chain. The possibility that this response is mediated by a receptor that is not coupled to FcR gamma-chain is excluded on the grounds that aggregation is absent in platelets from FcR gamma-chain-deficient mice.

L8 ANSWER 7 OF 18 MEDLINE DUPLICATE 5

2000417588 Document Number: 20393877. PubMed ID: 10933804. Isolation and characterization of EMS16, a C-lectin type protein from Echis multisquamatus venom, a potent and selective inhibitor of the alpha2beta1 integrin. Marcinkiewicz C; Lobb R R; Marcinkiewicz M M; Daniel J L; Smith J B; Dangelmaier C; Weinreb P H; Beacham D A; Niewiarowski S. (Sol Sherry Thrombosis Research Center, Department of Pharmacology, and Department of Physiology, Temple University, School of Medicine, 3400 North Broad Street, Philadelphia, Pennsylvania 19140, USA.. cmarcink@nimbus.temple.edu) . BIOCHEMISTRY, (2000 Aug 15) 39 (32) 9859-67.

Journal code: A0G; 0370623. ISSN: 0006-2960. Pub. country: United States.

Language: English.

AB We have isolated [redacted] characterized EMS16, a potent [redacted] selective inhibitor of the alpha2beta1 integrin, from Echis multisquamatus venom. It belongs to the family of C-lectin type of proteins (CLPs), and its amino acid sequence is homologous with other members of this protein family occurring in snake venoms. EMS16 (M(r) approximately 33K) is a heterodimer composed of two distinct subunits linked by S-S bonds. K562 cells transfected with alpha2 integrin selectively adhere to immobilized EMS16, but not to two other snake venom-derived CLPs, echicetin and alboaggregin B. EMS16 inhibits adhesion of alpha2beta1-expressing cells to immobilized collagen I at picomolar concentrations, and the platelet/collagen I interaction in solution at nanomolar concentrations. EMS16 inhibits binding of isolated, recombinant I domain of alpha2 integrin to collagen in an ELISA assay, but not the interaction of isolated I domain of alpha1 integrin with collagen IV. Studies with monoclonal **antibodies** suggested that EMS16 binds to the alpha2 subunit of the integrin. EMS16 inhibits collagen-induced platelet aggregation, but has no effect on aggregation induced by other agonists such as ADP, thromboxane analogue (U46619), TRAP, or **convulxin**. EMS16 also inhibits collagen-induced, but not **convulxin**-induced, platelet cytosolic Ca(2+) mobilization. In addition, EMS16 inhibits HUVEC migration in collagen I gel. In conclusion, we report a new, potent viper venom-derived inhibitor of alpha2beta1 integrin, which does not belong to the disintegrin family.

L8 ANSWER 8 OF 18 MEDLINE DUPLICATE 6

2000156004 Document Number: 20156004. PubMed ID: 10688826. Surface expression and functional characterization of alpha-granule factor V in human platelets: effects of ionophore A23187, thrombin, collagen, and **convulxin**. Alberio L; Safa O; Clemetson K J; Esmon C T; Dale G L. (W. K. Warren Medical Research Institute and Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City 73190, USA.)

BLOOD, (2000 Mar 1) 95 (5) 1694-702. Journal code: A8G; 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Factor V (FV) present in platelet alpha-granules has a significant but incompletely understood role in hemostasis. This report demonstrates that a fraction of platelets express very high levels of surface-bound, alpha-granule FV on simultaneous activation with 2 agonists, thrombin and **convulxin**, an activator of the collagen receptor glycoprotein VI. This subpopulation of activated platelets represents 30.7% +/- 4.7% of the total population and is referred to as **convulxin** and thrombin-induced-FV (COAT-FV) platelets. COAT-FV platelets are also observed on activation with thrombin plus collagen types I, V, or VI, but not with type III. No single agonist examined was able to produce COAT-FV platelets, although ionophore A23187 in conjunction with either thrombin or **convulxin** did generate this population. COAT-FV platelets bound annexin-V, indicating exposure of aminophospholipids and were enriched in young platelets as identified by the binding of thiazole orange. The functional significance of COAT-FV platelets was investigated by demonstrating that factor Xa preferentially bound to COAT-FV platelets, that COAT-FV platelets had more FV activity than either thrombin or A23187-activated platelets, and that COAT-FV platelets were capable of generating more prothrombinase activity than any other physiologic agonist examined. Microparticle production by dual stimulation with thrombin and **convulxin** was less than that observed with A23187, indicating that microparticles were not responsible for all the activities observed. These data demonstrate a new procoagulant component produced from dual

stimulation of platelets with thrombin and collagen. COAT-FV platelets may explain the unique role of alpha-granule FV and the hemostatic effectiveness of young platelets. (Blood. 2000;95:1694-1702)

L8 ANSWER 9 OF 18 MEDLINE DUPLICATE 7
2000132875 Document Number: 20132875. PubMed ID: 10666318. Distinct contributions of glycoprotein VI and alpha(2)beta(1) integrin to the induction of platelet protein tyrosine phosphorylation and aggregation. Kamiguti A S; Theakston R D; Watson S P; Bon C; Laing G D; Zuzel M. (Department of Haematology, Royal Liverpool Hospital, Liverpool, United Kingdom.. aurakami@liverpool.ac.uk) . ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (2000 Feb 15) 374 (2) 356-62. Journal code: 6SK; 0372430. ISSN: 0003-9861. Pub. country: United States. Language: English.
AB Platelet activation by collagen depends principally on two receptors, alpha(2)beta(1) integrin (GPIa-IIa) and GPVI. During this activation, the nonreceptor protein tyrosine kinase pp72(syk) is rapidly phosphorylated, but the precise contribution of alpha(2)beta(1) integrin and GPVI to signaling for this phosphorylation is not clear. We have recently found that proteolysis of platelet alpha(2)beta(1) integrin by the snake venom metalloproteinase, jararhagin, results in inhibition of collagen-induced platelet aggregation and pp72(syk) phosphorylation. In order to verify whether the treatment of platelets with jararhagin had any effect on GPVI signaling, in this study we stimulated platelets treated with either jararhagin or anti-alpha(2)beta(1) **antibody** with two GPVI agonists, an **antibody** to GPVI and **convulxin**. Platelet shape change and phosphorylation of pp72(syk) by both GPVI agonists was preserved, as was the structure and function of GPVI shown by (125)I-labeled **convulxin** binding to immunoprecipitated GPVI from jararhagin-treated platelets. In contrast, defective platelet aggregation in response to GPVI agonists occurred in both jararhagin-treated and alpha(2)beta(1)-blocked platelets. This apparent cosignaling role of alpha(2)beta(1) integrin for platelet aggregation suggests the possibility of a topographical association of this integrin with GPVI. We found that both platelet alpha(2)beta(1) integrin and GPVI coimmunoprecipitated with alpha(IIb)beta(3) integrin. Since platelet aggregation requires activation of alpha(IIb)beta(3) integrin, defective aggregation in the absence of alpha(2)beta(1) suggests that this receptor may provide a signaling link between GPVI and alpha(IIb)beta(3). Our study therefore demonstrates that platelet signaling leading to pp72(syk) phosphorylation initiated with GPVI engagement by either **convulxin** or GPVI **antibody** does not depend on alpha(2)beta(1) integrin. However, alpha(IIb)beta(3) integrin may, in this model, require functional alpha(2)beta(1) integrin for its activation.

L8 ANSWER 10 OF 18 MEDLINE DUPLICATE 8
2000474813 Document Number: 20284011. PubMed ID: 10822077. Cloning and expression of the platelet-specific collagen receptor glycoprotein VI. Miura Y; Ohnuma M; Jung S M; Moroi M. (Department of Protein Biochemistry, Institute of Life Science, Kurume University, Fukuoka, Japan.) THROMBOSIS RESEARCH, (2000 May 15) 98 (4) 301-9. Journal code: VRN; 0326377. ISSN: 0049-3848. Pub. country: United States. Language: English.
AB Platelet glycoprotein VI (GP VI) was purified from platelet membranes and its internal amino acid sequences were determined. The cloned cDNA of GP VI indicates an open reading frame coding for 20 amino acid signal sequences and a mature protein of 319 amino acids. Its extracellular region has two Ig-like domains and a mucin-like, Ser/Thr-rich region, suggesting that GP VI is a member of the paired Ig-like receptor family. GP VI-transfected cells contained **convulxin**-(reactive) and

antibody against recombinant GP VI-reactive protein bands that migrated at the same position as platelet GP VI in SDS/PAGE-electroblotting. These data indicate that the protein deduced from the cloned cDNA corresponds to platelet GP VI.

L8 ANSWER 11 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
2001:311372 Document No.: PREV200100311372. Coat-platelets: High levels of adhesive and procoagulant proteins on cell surface require transglutaminase activity. Dale, George L. (1); Friese, Paul (1); Batar, Peter (1); Reed, Guy L.; Clemetson, Kenneth J.; Alberio, Lorenzo. (1) Medicine, Univ. Okla. Health Sci. Cntr., Oklahoma City, OK USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 52b-53b. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology. ISSN: 0006-4971. Language: English. Summary Language: English.
AB A sub-population of platelets stimulated with thrombin plus **convulxin**, a glycoprotein VI specific agonist, demonstrate high levels of alpha-granule factor V (FV); these cells were referred to as COAT-platelets (collagen/**convulxin** and thrombin activated platelets; BLOOD 95:1694, 2000). COAT-platelets also express additional alpha-granule proteins on their surface including fibrinogen, von Willebrand factor, thrombospondin, fibronectin and alpha-2-antiplasmin. All of these proteins are substrates for transglutaminases, and accordingly, the production of COAT-platelets can be prevented by a number of competitive inhibitors of transglutaminases including dansyl cadaverine, putrescine, acetylated-casein and a synthetic peptide (CP15) corresponding to the glutamine-donor sequence of betacasein. In addition, inclusion of biotinylated-CP15 during COAT-platelet production resulted in its attachment to the cells in a manner similar to that observed with alpha-granule proteins. A monoclonal **antibody** against tissue transglutaminase indicated the presence of this enzyme on the surface of COAT-platelets. Staining of COAT-platelets with anti-factor XIII **antibodies** demonstrated a more modest, variable labeling; however, two **antibodies**, 9C11 and R2, that inhibit FXIIIa activation and activity, respectively, decreased COAT-platelet generation. These data indicate that COAT-platelets express high levels of procoagulant and adhesive molecules on their surface and that one or more transglutaminase activities are involved in production of COAT-platelets. COAT-platelets represent a previously unrecognized component of the hemostatic process with the potential to impact both the cellular and fluid phases of hemostasis.

L8 ANSWER 12 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
2001:311349 Document No.: PREV200100311349. Coat-platelets are generated by co-stimulation of the thrombin and Fc receptors. Batar, Peter (1); Dale, George L. (1). (1) Medicine and W.K. Warren Med. Res. Inst., OU Health Sci. Cntr., Oklahoma City, OK USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 48b. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology. ISSN: 0006-4971. Language: English. Summary Language: English.
AB COAT-Platelets (collagen and thrombin activated platelets; BLOOD 95:1694, 2000) represent a unique subset of activated platelets binding high levels of adhesive and procoagulant alpha-granule proteins on their surface. The exact agonist requirements for COAT-platelet formation have not been defined although it seemed likely that Fc receptor (FcgammaRIIA; CD32) stimulation might substitute for collagen since the glycoprotein VI collagen receptor involved in COAT-platelet formation shares several signaling pathways with FcgammaRIIA. In this report we demonstrate that

COAT-platelets can be generated by FcgammaRIIA engagement in conjunction with thrombin activation. FcgammaRIIA activation was achieved either with anti-CD9 monoclonal **antibodies** (ALB6 and ML13) or by direct Fc receptor cross-linking using an anti-CD32 mAb, IV.3, and a goat-anti-mouse-IgG (GAMG) polyclonal **antibody**. While both methods of FcgammaRIIA engagement resulted in platelet activation, COAT-platelets were only observed upon simultaneous activation with thrombin. COAT-platelets formed with FcgammaRIIA activation and thrombin shared many characteristics with previously described COAT-platelets including exposure of aminophospholipids, presence of procoagulant and adhesive proteins on their surface, enrichment among young cells and sensitivity to transglutaminase inhibitors. The average percentage of COAT-platelets observed with thrombin plus FcgammaRIIA stimulation was 10.8% +- 4.2% (n=87) which was 46.5% of that observed with thrombin plus **convulxin**. In addition, the time dependence for dual stimulation was monitored. In contrast to thrombin plus **convulxin** where nearly simultaneous activation is essential for COAT-platelet formation, stimulation of FcgammaRIIA with ALB6 together with thrombin allowed for a time delay of either agonist of up to 2 minutes without any effect on the percentage of COAT-platelets formed. Stimulation with thrombin followed by

IV.3/GAMG similarly was time independent under the conditions studied; however, IV.3/GAMG stimulation followed by thrombin resulted in a substantial loss of COAT-platelet formation within 60 seconds of the initial stimulation. The formation of COAT-platelets upon Fc receptor engagement and thrombin exposure provides the first example where these procoagulant platelets are likely to be formed under pathological rather than physiological conditions.

L8 ANSWER 13 OF 18 MEDLINE DUPLICATE 9

1999436101 Document Number: 99436101. PubMed ID: 10506151. The platelet collagen receptor glycoprotein VI is a member of the immunoglobulin superfamily closely related to FcalphaR and the natural killer receptors. Clemetson J M; Polgar J; Magnenat E; Wells T N; Clemetson K J. (Theodor Kocher Institute, University of Berne, Freiestrasse 1, CH-3012 Berne, Switzerland.. clemetson@tki.unibe.ch) . JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Oct 8) 274 (41) 29019-24. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB We have cloned the platelet collagen receptor glycoprotein (GP) VI from a human bone marrow cDNA library using rapid amplification of cDNA ends with

platelet mRNA to complete the 5' end sequence. GPVI was isolated from platelets using affinity chromatography on the snake C-type lectin, **convulxin**, as a critical step. Internal peptide sequences were obtained, and degenerate primers were designed to amplify a fragment of the GPVI cDNA, which was then used as a probe to screen the library. Purified GPVI, as well as Fab fragments of polyclonal **antibodies** made against the receptor, inhibited collagen-induced platelet aggregation. The GPVI receptor cDNA has an open reading frame of 1017 base

pairs coding for a protein of 339 amino acids including a putative 23-amino acid signal sequence and a 19-amino acid transmembrane domain between residues 247 and 265. GPVI belongs to the immunoglobulin superfamily, and its sequence is closely related to FcalphaR and to the natural killer receptors. Its extracellular chain has two Ig-C2-like domains formed by disulfide bridges. An arginine residue is found in position 3 of the transmembrane portion, which should permit association with Fcgamma and its immunoreceptor tyrosine-based activation motif via a salt bridge. With 51 amino acids, the cytoplasmic tail is relatively long and shows little homology to the C-terminal part of the other family members. The ability of the cloned GPVI cDNA to code for a functional platelet collagen receptor was demonstrated in the megakaryocytic cell line Dami. Dami cells transfected with GPVI cDNA mobilized intracellular Ca(2+) in response to collagen, unlike the nontransfected or mock

transfected Dami cells, which do not respond to collagen.

L8 ANSWER 14 OF 18 MEDLINE DUPLICATE 10
1998336213 Document Number: 98336213. PubMed ID: 9670039. Physical and functional association of the Src family kinases Fyn and Lyn with the collagen receptor glycoprotein VI-Fc receptor gamma chain complex on human platelets. Ezumi Y; Shindoh K; Tsuji M; Takayama H. (Department of Hematology and Oncology, Clinical Sciences for Pathological Organs, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan.) JOURNAL OF EXPERIMENTAL MEDICINE, (1998 Jul 20) 188 (2) 267-76. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB We have previously shown that uncharacterized glycoprotein VI (GPVI), which is constitutively associated and coexpressed with Fc receptor gamma chain (FcRgamma) in human platelets, is essential for collagen-stimulated tyrosine phosphorylation of FcRgamma, Syk, and phospholipase Cgamma2 (PLCgamma2), leading to platelet activation. Here we investigated involvement of the Src family in the proximal signals through the GPVI-FcRgamma complex, using the snake venom **convulxin** from Crotalus durissus terrificus, which specifically recognizes GPVI and activates platelets through cross-linking GPVI. **Convulxin** -coupled beads precipitated the GPVI-FcRgamma complex from platelet lysates. Collagen and **convulxin** induced tyrosine phosphorylation of FcRgamma, Syk, and PLCgamma2 and recruited tyrosine-phosphorylated Syk to the GPVI-FcRgamma complex. Using coprecipitation methods with **convulxin**-coupled beads and **antibodies** against FcRgamma and the Src family, we showed that Fyn and Lyn, but not Yes, Src, Fgr, Hck, and Lck, were physically associated with the GPVI-FcRgamma complex irrespective of stimulation. Furthermore, Fyn was rapidly activated by collagen or cross-linking GPVI. The Src family-specific inhibitor PP1 dose-dependently inhibited collagen- or **convulxin**-induced tyrosine phosphorylation of proteins including FcRgamma, Syk, and PLCgamma2, accompanied by a loss of aggregation and ATP release reaction. These results indicate that the Src family plays a critical role in platelet activation via the collagen receptor GPVI-FcRgamma complex.

L8 ANSWER 15 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 11
1998228355 EMBASE **Convulxin**-induced platelet adhesion and aggregation: Involvement of glycoproteins VI and IaIIa. Jandrot-Perrus M.;
Lagrue A.H.; Leduc M.; Okuma M.; Bon C.. Dr. M. Jandrot-Perrus, Lab. Recherche Hemostase Thrombose, Faculte de Medecine Xavier Bichat, 75870 Paris Cedex 18, France. Platelets 9/3-4 (207-211) 1998.
Refs: 22.
ISSN: 0953-7104. CODEN: PLTEEF. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The interaction of **convulxin** (Cvx), a 72-kDa glycoprotein isolated from the venom of Crotalus durissus terrificus with human platelets has been studied. Cvx at low concentrations (below 100 pM) induced platelet aggregation, dense body secretion and intracellular calcium mobilization which indicates that Cvx is a potent activator of human platelets. Cvx-induced platelet aggregation and secretion was inhibited by 6F1 an anti-integrin .alpha.2.beta.1 monoclonal **antibody** that was without effect on calcium mobilization. Anti-GPVI Fab fragments inhibited aggregation, secretion and calcium mobilization triggered by Cvx. In addition, immobilized Cvx was found to induce divalent cation-independent platelet adhesion in a static system. Platelet adhesion to Cvx was inhibited by anti-GPVI Fab fragments but not by anti-integrin .alpha.2.beta.1. Cvx was shown to bind to a 57,000 Dalton protein that was identified as GPVI. Altogether, these results indicate that GPVI behaves as a receptor for Cvx, while integrin .alpha.2.beta.1 could play a regulatory role in Cvx-induced platelet aggregation. Cvx and

collagen interaction with platelets, thus appears to share some characteristics [redacted] to also have specific propert[redacted].

L8 ANSWER 16 OF 18 MEDLINE DUPLICATE 12
1998001677 Document Number: 98001677. PubMed ID: 9341142. Adhesion and activation of human platelets induced by **convulxin** involve glycoprotein VI and integrin alpha2beta1. Jandrot-Perrus M; Lagrue A H; Okuma M; Bon C. (Laboratoire de Recherche sur l'Hemostase et la Thrombose, Faculte de Medecine Xavier Bichat, BP 416, 75870 Paris Cedex 18, France.)
JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Oct 24) 272 (43) 27035-41. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB We analyzed the interaction of **convulxin** (Cvx), a 72-kDa protein isolated from the venom of Crotalus durissus terrificus, with human platelets. Cvx is a potent platelet agonist that induces an increase in the intracellular Ca2+ concentration ([Ca2+]i), granule exocytosis and aggregation. 125I-Labeled Cvx binds specifically and rapidly to platelets at binding sites of high and moderate affinity. Platelets adhere to immobilized Cvx in a time-dependent but cation-independent manner. Platelet exocytosis and aggregation induced by Cvx were inhibited by an anti-integrin alpha2beta1 monoclonal **antibody** (6F1) and by the Fab fragments of a polyclonal anti-glycoprotein VI (GPVI) **antibody**. Both the adhesion of platelets to Cvx and the Cvx-induced increase in [Ca2+]i were inhibited by anti-GPVI Fab fragments but not by 6F1. Ligand blotting assay showed that 125I-Cvx binds to a 57-kDa platelet protein with an electrophoretic mobility identical to that of GPVI. In addition, we observed the following: (i) 125I-Cvx binds to GPVI immunoprecipitated by the anti-GPVI **antibody** from a platelet lysate, and (ii) Cvx inhibits the binding of anti-GPVI IgG to GPVI. Taken together, these results demonstrate that GPVI behaves as a Cvx receptor and that the alpha2beta1 integrin appears to be involved in the later stages of Cvx-induced platelet activation, i.e. exocytosis and aggregation.

L8 ANSWER 17 OF 18 MEDLINE DUPLICATE 13
97298057 Document Number: 97298057. PubMed ID: 9153205. Platelet activation and signal transduction by **convulxin**, a C-type lectin from Crotalus durissus terrificus (tropical rattlesnake) venom via the p62/GPVI collagen receptor. Polgar J; Clemetson J M; Kehrel B E; Wiedemann M; Magnenat E M; Wells T N; Clemetson K J. (Theodor Kocher Institute, University of Berne, Freiestrasse 1, CH-3012 Berne, Switzerland.)
JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 May 23) 272 (21) 13576-83. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB **Convulxin**, a powerful platelet activator, was isolated from Crotalus durissus terrificus venom, and 20 amino acid N-terminal sequences of both subunits were determined. These indicated that **convulxin** belongs to the heterodimeric C-type lectin family. Neither **antibodies** against GPIb nor echicetin had any effect on **convulxin**-induced platelet aggregation showing that, in contrast to other venom C-type lectins acting on platelets, GPIb is not involved in **convulxin**-induced platelet activation. In addition, partially reduced/denatured **convulxin** only affects collagen-induced platelet aggregation. The mechanism of **convulxin**-induced platelet activation was examined by platelet aggregation, detection of time-dependent tyrosine phosphorylation of platelet proteins, and binding studies with 125I-**convulxin**. **Convulxin** induces signal transduction in part like collagen, involving the time-dependent tyrosine

phosphorylation of Fc receptor gamma chain, phospholipase Cgamma2, p72(SYK), c-Cbl, and p36-38. However, unlike collagen, pp125(FAK) and some other bands are not tyrosine-phosphorylated. **Convulxin** binds to a glycosylated 62-kDa membrane component in platelet lysate and to p62/GPVI immunoprecipitated by human anti-p62/GPVI **antibodies**. **Convulxin** subunits inhibit both aggregation and tyrosine phosphorylation in response to collagen. Piceatannol, a tyrosine kinase inhibitor with some specificity for p72(SYK), showed differential effects on collagen and **convulxin**-stimulated signaling. These results suggest that **convulxin** uses the p62/GPVI but not the alpha2beta1 part of the collagen signaling pathways to activate platelets. Occupation and clustering of p62/GPVI may activate Src family kinases phosphorylating Fc receptor gamma chain and, by a mechanism previously described in T- and B-cells, activate p72(SYK) that is critical for downstream activation of platelets.

L8 ANSWER 18 OF 18 MEDLINE
86159939 Document Number: 86159939. PubMed ID: 3938295. Isolation and characterization of the alpha and beta subunits of the platelet-activating glycoprotein from the venom of Crotalus durissus cascavella. Marlas G. BIOCHIMIE, (1985 Dec) 67 (12) 1231-9. Journal code: A14; 1264604. ISSN: 0300-9084. Pub. country: France. Language: English.
AB It was concluded in a previous paper that the high Mr platelet-activating glycoprotein isolated earlier from the venom of Crotalus durissus cascavella has an hexameric structure of the alpha 3 beta 3 type involving two distinct subunits. Data reported here demonstrate that these two subunits are separable from each other by ion exchange chromatography under denaturating conditions, have similar Mrs (alpha = 12,540 et beta = 13,770) and exist in a one to one ratio within the native molecule. Carbohydrate analysis indicated that they are both similarly glycosylated to a small extent. They have slightly different amino-acid compositions, a common N-terminal sequence up to the fifth residue and similar extinction coefficients at 280 nm. The native molecule has a calculated Mr of 78,930. Additional data demonstrated that **convulxin** from the venom of Crotalus durissus terrificus is the same platelet-activating agent as the presently described platelet-activating glycoprotein (PAG) from the venom of Crotalus durissus cascavella.

=> s (busfield s?/au or villeval j?/au or jamdrot perrus m?/au or vainchencker w?/au or gill d?/au or qian m?/au or kingbury g?/au)

L9 4678 (BUSFIELD S?/AU OR VILLEVAL J?/AU OR JAMDROT PERRUS M?/AU OR VAINCHENCKER W?/AU OR GILL D?/AU OR QIAN M?/AU OR KINGBURY G?/AU)

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L10 8 L9 AND TANGO

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PROCESSING COMPLETED FOR L10
L11 8 DUP REMOVE L10 (0 DUPLICATES REMOVED)

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L11 ANSWER 1 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
2001:513896 Document No.: PREV200100513896. Molecules of the herpesvirus-entry-mediator-related protein family and uses thereof. **Busfield, Samantha J.**. ASSIGNEE: Millennium Pharmaceuticals, Inc.. Patent Info.: US 6287808 September 11, 2001. Official Gazette of the United States Patent and Trademark Office Patents, (Sep. 11, 2001) Vol. 1250, No. 2, pp. No Pagination. e-file. ISSN: 0098-1133. Language: English.

AB Novel **TANGO**-69-receptor polypeptides, proteins, and nucleic acid molecules are disclosed. In addition to isolated, full-length **TANGO**-69-receptor proteins, the invention further provides isolated **TANGO**-69-receptor fusion proteins, antigenic peptides and anti-**TANGO**-69-receptor antibodies. The invention also provides **TANGO**-69-receptor nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals in which a **TANGO**-69-receptor gene has been introduced or disrupted. Diagnostic, screening and therapeutic methods utilizing compositions of the invention are also provided.

L11 ANSWER 2 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
2001:339372 Document No.: PREV200100339372. Nucleic acid molecules encoding glycoprotein VI and recombinant uses thereof. **Busfield, Samantha J.**; **Villeval, Jean-Luc (1)**. (1) Needham, MA USA. ASSIGNEE: Millennium Pharmaceuticals, Inc.. Patent Info.: US 6245527 June 12, 2001. Official Gazette of the United States Patent and Trademark Office Patents,
(June 12, 2001) Vol. 1247, No. 2, pp. No Pagination. e-file. ISSN: 0098-1133. Language: English.

AB The invention provides isolated **TANGO** 268 nucleic acid molecules and polypeptide molecules. **TANGO** 268 encodes a polypeptide that represents glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The invention also provides antisense nucleic acid molecules, expression vectors containing the nucleic acid molecules of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid molecule of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compositions of the invention are also provided.

L11 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2001 ACS
2001:12605 Document No. 134:81775 Glycoprotein VI cDNA and protein from human and murine blood platelets and their diagnostic and therapeutic applications. **Busfield, Samantha J.**; Villelal, Jean-luc; Jandrot-Perrus, Martine; **Vainchencker, William**; **Gill, Davinder Singh**; **Qian, Ming Diana**; Kingsbury, Gillian (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2001000810 A1 20010104, 227 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US18152 20000630. PRIORITY: US 1999-345468 19990630; US 1999-454824 19991206; US 2000-503387 20000214.

AB The invention provides isolated cDNA mols. and polypeptide mols. that encode human and murine glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The protein initially

designated **TANGO** 268 represents the platelet-expressed collagen receptor glycoprotein VI (GPVI) based on the following evidence: (1) the glycosylated mol. wts. of **TANGO** 268 and GPVI are identical or similar; (2) both are recognized by anti-GPVI antibodies and bind to convulxin; (3) both are preferentially expressed in megakaryocytic cells; (4) both ar predicted to have a single N-glycosylation site; (5) the mol. mass of GPVI upon N- and O-linked glycosylation is .apprx.62 kDa, that of GPVI; (6) two Ig-like domains in **TANGO** 268 indicates interaction with FcR.gamma.; (7) the absence of a large intracytoplasmic tail suggests that this membrane-bound glycoprotein has no signaling role but assocs. with another member of the Ig family; and (8) **TANGO** 268 has a charged arginine residue in the transmembrane domain which is also predicted to be present in GPVI. The human gene for GPVI was mapped on radiation hybrid panels to the long arm of chromosome 19, in the region 19q13, syntenic to mouse chromosome 7. The invention also provides antisense nucleic acid mols., expression vectors contg. the nucleic acid mols. of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid mol. of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

L11 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2001 ACS

2001:12497 Document No. 134:81747 Membrane-associated and secreted proteins identified by sequence similarity and their possible therapeutic uses. Barnes, Thomas M.; Fraser, Christopher C.; Wrighton, Nicholas; Myers, Paul; **Busfield, Samantha J.**; Sharp, John D. (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2001000673 A1 20010104, 294 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US18198 20000629. PRIORITY: US 1999-345464 19990630.

AB The invention provides isolated nucleic acid mols., designated INTERCEPT 340, MANGO 003, MANGO 347, **TANGO** 272, **TANGO** 295, **TANGO** 354, and **TANGO** 378 which encode wholly secreted or membrane-assocd. proteins. The invention also provides antisense nucleic acid mols., expression vectors contg. the nucleic acid mols. of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid mol. of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

L11 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2001 ACS

2000:457098 Document No. 133:103730 Class II cytokine receptor-like proteins and nucleic acids encoding them. **Busfield, Samantha J.** (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2000039161 A1 20000706, 127 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US31328 19991230.

PRIORITY: US 1998-224669 19981231.

AB The invention pr[redacted]des isolated nucleic acid mols [redacted]designated **TANGO** 241 and **TAN**[redacted] 242. These nucleic acid mols. encode transmembrane proteins that bear substantially sequence similarity to members of the type II cytokine receptor family. The invention also provides antisense nucleic acid mols., expression vectors contg. the nucleic acid mols. of the invention, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a nucleic acid mol. of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided. The nucleic acids and polypeptides of the present invention are useful as modulating agents in regulating a variety of cellular processes.

L11 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2001 ACS

2000:227685 Document No. 132:278190 Novel secreted immunomodulatory proteins and uses thereof. **Busfield, Samantha J.** (Millennium Biotherapeutics, Inc., USA). PCT Int. Appl. WO 2000018800 A1 20000406, 122 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US22818 19990930. PRIORITY: US 1998-163523 19980930.

AB The invention concerns cDNA mols. encoding **TANGO** 191 and **TANGO** 195, both of which are transmembrane proteins. Human **TANGO** 19 appears to be a member of the interleukin 1 receptor superfamily, while **TANGO** 195 belongs to the CD2 subgroup of the Ig. superfamily. The nucleic acids and polypeptides of the present invention are useful as modulating agents in regulating a variety of cellular processes, and for treating immunol. disorders, inflammatory diseases, allergies, and autoimmune diseases. Accordingly, in one aspect, this invention provides isolated nucleic acid mols. encoding a polypeptide of the invention or biol. active portion thereof. The present invention also provides nucleic acid mols. which are suitable as primers or hybridization probes for the detection of nucleic acids encoding a polypeptide of the invention.

L11 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2001 ACS

2000:175929 Document No. 132:218642 Novel molecules of the herpes virus-entry-mediator-related protein family and their diagnostic and therapeutic uses. **Busfield, Samantha J.** (Millennium Biotherapeutics, Inc., USA). PCT Int. Appl. WO 2000014230 A1 20000316, 151 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US20180 19990903. PRIORITY: US 1998-146950 19980903; US 1999-342767 19990629.

AB The present invention is based on the discovery of 3 cDNA mols. which encode sol. forms (sHVEM), and one cDNA mol. that encodes a second membrane-bound form, of the membrane-bound herpes virus entry mediator

(mHVEM), a member of the tumor necrosis factor receptor superfamily. The 3 sHVEM sequences differ from mHVEM in 2 important ways: first they lac the C-terminal end of mHVEM which contains the transmembrane domain of mHVEM; and secondly, they have addnl. amino acids at their C-terminal ends
that are not found at the C-terminal end of mHVEM. The HVEM mols. bind to
LIGHT (also called **TANGO**-69) and lymphotoxin a, such that the mols. are also known as **TANGO**-69 receptors. Northern blot anal. revealed that an .apprx.2 kb sHVEM1 mRNA transcript is present at similar levels in stimulated and unstimulated mast cells, as well as in stimulated
human umbilical vein endothelial cells (HUVECs), but not in unstimulated HUVECs. Tissue localization suggests that sHVEM1 can play a role in allergic reactions and can play an anti-inflammatory role in the endothelium. Mapping data places **TANGO**-69 receptor gene at human chromosome 1 region p36.2-p36.3, an area putatively syntenic to a region of mouse chromosome 4 near the IgE defective response locus. In addn. to isolated, full-length **TANGO**-69-receptor proteins, the invention further provides isolated **TANGO**-69-receptor fusion proteins, antigenic peptides and anti-**TANGO**-69-receptor antibodies. The invention also provides **TANGO**-69-receptor nucleic acid mols., recombinant expression vectors contg. a nucleic acid mol. of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals in which a **TANGO**-69-receptor gene has been introduced or disrupted. Diagnostic, screening
and therapeutic methods utilizing compns. of the invention are also provided.

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1999:184273 Document No. 130:222134 Murine **TANGO**-69 is a novel member of the tumor necrosis factor receptor ligand-related protein family. **Busfield, Samantha J.** (Millennium Biotherapeutics, Inc., USA). PCT Int. Appl. WO 9911662 A1 19990311, 127 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US18533 19980903. PRIORITY: US 1997-57936 19970905.
AB Novel murine **TANGO**-69 nucleic acid mols. and polypeptides are disclosed. The 1.9-kb cDNA encodes a protein of 239 amino acids which is a type II membrane protein that is predicted to be the murine homolog of the human HVEM ligand, LIGHT. Alignment of murine **TANGO**-69 with human Fas ligand reveals 30% identity at the nucleotide level and 54% identity at the amino acid level. Northern anal. reveals that **TANGO**-69 is expressed as an .apprx.2-kb transcript in the spleen and lung and and a .apprx.1.4-kb transcript in the heart and skeletal muscle. **TANGO**-69 binds masts cells, up-regulates prodn. of IL-4 in response to anti-CD3, up-regulates E-selectin and VCAM-1, and induces synthesis of IL-8 in HUVEC cells. The murine gene was mapped to chromosome 17 between the 2 markers D17MIT9 and D17MIT39. In addn., the invention provides isolated **TANGO**-69 fusion proteins, antigenic peptides and anti-**TANGO**-69 antibodies. The invention also provides **TANGO**-69 recombinant expression vectors contg. nucleic acid mols. of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals in which a **TANGO**-69 gene has been introduced or disrupted. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

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Executing the logoff script...

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	77.83	77.98

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-5.88	-5.88

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